A Prostate Cancer Susceptibility Region Also Impacts Colorectal Cancer Risk

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Genome-wide association studies have identified hundreds of common genetic variants that collectively impact risk for a wide variety of cancers. In some cases, the same genetic variant impacts risk for multiple cancer types. Such shared genetic associations between diseases (i.e. pleiotropy) can suggest shared biological mechanisms or novel molecular pathways. Evaluating previous genetic findings for additional pleiotropic relationships is an emerging strategy for identifying new genetic risk factors for disease. Together with an international collaboration of researchers, Drs. Jonathan M. Kocarnik and Ulrike Peters in the Public Health Sciences Division recently reported their findings from such an analysis in the journal *Gut*.

Looking for pleiotropic relationships with colorectal cancer, the researchers evaluated 171 single nucleotide polymorphisms (SNPs) previously implicated as risk variants for 18 different cancers. To improve the possibility of finding such novel relationships, data collected by three large consortia were combined: the Colon Cancer Family Registry (CCFR), the Genetics and Epidemiology of Colorectal Cancer study (GECCO), and the Population Architecture using Genomics and Epidemiology study (PAGE). With 16 studies participating through one or more of these consortia, this collaboration meant a large sample size of approximately 13,000 colorectal cancer cases and 41,000 controls.

Meta-analyses across these participating studies identified two correlated SNPs demonstrating a statistically significant relationship with colorectal cancer (top SNP Odds Ratio = 1.12, P-value = 0.00002). Previously associated with prostate cancer, these SNPs are located in region 1 of the 8q24 section of the genome. Distinct regions on this portion of chromosome 8 have been associated with a number of cancer types, and are thought to impact cancer risk through long-range tissue-specific enhancers that physically interact with the MYC oncogene. While region 3 of 8q24 has consistently been associated with colorectal cancer risk, region 1 has not previously been implicated despite multiple previous investigations, all of smaller sample size. In this study, additional analyses provided support that these two SNPs in region 1 are novel findings for colorectal cancer risk, and demonstrated similar associations across racial/ethnic populations and anatomical sub-sites.

In addition to these novel findings, the authors also provided supportive evidence to previous findings that a glioma SNP in the TERT gene is associated with colorectal cancer. TERT, which encodes for telomerase reverse transcriptase, is another gene region that has been implicated for several different cancers. Interestingly, the genetic effect of this SNP appears to vary in direction, with the same allele associated with a decreased risk for some cancers but an increased risk for others. Identification of such opposing pleiotropic effects may suggest context-specific differences in gene regulation or other molecular differences.

Both findings in this study contribute to the growing evidence of pleiotropic relationships at these loci, and demonstrate the benefit of evaluating known genetic variants for novel pleiotropic relationships. According to co-senior author Dr. Ulrike Peters, such evaluations are important because "identifying these pleiotropic effects of genes suggest that these genes are involved in key carcinogenic processes." Adds co-lead author Dr. Jonathan M. Kocarnik, "such pleiotropic variants may help not only in elucidating disease-specific risk, but also help move towards a more comprehensive understanding of genetic risk across broad classes of disease." Eventually, variants such as those identified in this study might be utilized to help identify and select high-risk populations for targeted screening.

Both Drs. Kocarnik and Peters emphasized that collaboration with other groups was a major contributor to the success of this paper. Peters states that it is "thanks to the willingness of many investigators across North America, Australia, and Europe to collaborate and combine their samples that this study had substantial power to identify genetic effects that impact multiple cancers." In addition, "the cooperation and communication across so many studies was fantastic," says Kocarnik, "and is a testament to the productive power of team science."

Additional investigators in Public Health Sciences contributing to this project included Drs. Chris S. Carlson, Polly A. Newcomb, Li Hsu, Charles Kooperberg, and Emily White, with additional support from Yi Lin, Cara L. Carty, Sue Mann, Shuo Jiao, and Tabitha A. Harrison.

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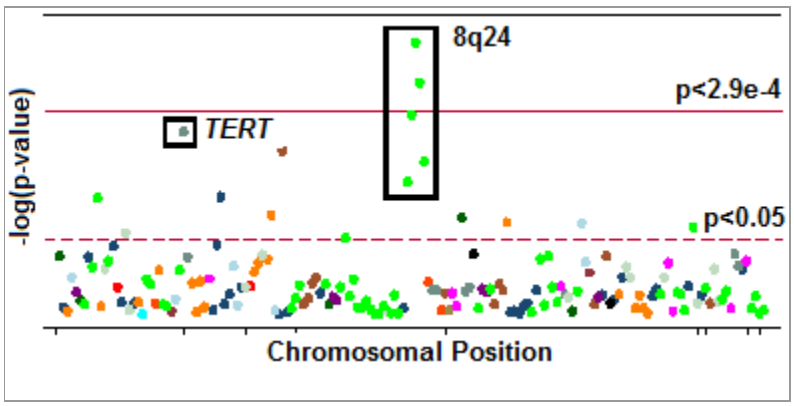

Image provided by Jonathan Kocarnik.

Manhattan plot of the association between colorectal cancer and genetic risk variants previously identified for other cancers. Two variants in the 8q24 region showed novel statistically significant associations with colorectal cancer, while one variant in the TERT gene suggested support for a previously reported association with colorectal cancer.